

Liver Transplantation

T. E. Starzl
(Denver, U.S.A.)

Prof. Stefanini, Ladies and Gentlemen,

before beginning I would like to thank your Society for the privilege of visiting your beautiful and modern country and also for being able to see so many old friends.

This morning I will simply talk about our more recent experience with orthotopic liver transplantation. In a way it is a pity to do just this, because there was a tremendous background of experimental work that went into the field of liver transplantation and which — I think — contributed to a general improvement of the care that could be given to recipients of kidneys of or other organs, but we will have to pass over this because of the limitations of time.

To begin with the feasibility of performing liver replacement, that is removing a liver and placing another one in a dog, with chronic survival — that proof was provided about five years ago, when the first animals survived this operation and some of these dogs are still alive.

A curious thing was seen in this really successful experience and that was that it was possible in many of the dogs to stop therapy and have the dogs alive for many months or many years. In some subsequent work with antilymphocyte serum or globulin, it was observed that a half dozen or so injections in some dogs were all that were required to permit chronic survival or survival for a year or a year and a half. One of our animals was treated only pre-operatively, some others were treated for only some two or three weeks after operation and then lived for a year afterwards, having received an orthotopic homograft. So that there is implicit, in this type of experiment and in this sort of finding, the notion that tolerance was accidentally created.

Well, perhaps we can save sometimes by going into the statistics at our institutions and there are others about clinical orthotopic liver transplantation.

Such an attempt was first made in the spring of 1963 and between that time and the summer of 1967 there had been nine reported — or at least known: seven in Denver and one each in Boston at the Peter Bent Brigham Hospital and in Paris, the latter being done by Prof. Demirleau.



FIG. 1

This is one of the dogs. This dog was actually treated in March of 1964, so he is going to be five years in a few months — the animal is still alive, having had his liver removed and then replaced with that of a non-related mongrel donor (fig. 1).

Unfortunately the transfer of this kind of experience to the care of sick patients was not all that easy, and one of the reasons of course is that the livers that had to be removed in the patients were afflicted with a serious pathology. This is an example of a patient who had a hepatoma, a little girl about 18 months old, who had a hepatoma diagnosed at operation in February 1967. And by the time that the liver replacement could be carried out a few months later, you can see the extent of the growth of the tumour; at the time of its removal this weighed about 1500 grams, in a child whose liver should have weighed about 200 or 250 grams.

N
about
transpl
longest

TH
variatio
is a hi
populat
recipien
the oth
about 4
in whic
the por
the live
A and
artery o
artery o
to the s
in the d

Now, this is what an hepatoma may look like, this is a liver weighing about 20 lb. It was removed from a 28-year-old girl submitted to orthotopic transplantation in 1964, and the recipient died in 23 days — it was the longest survival of any of the cases that I described — in the first series.

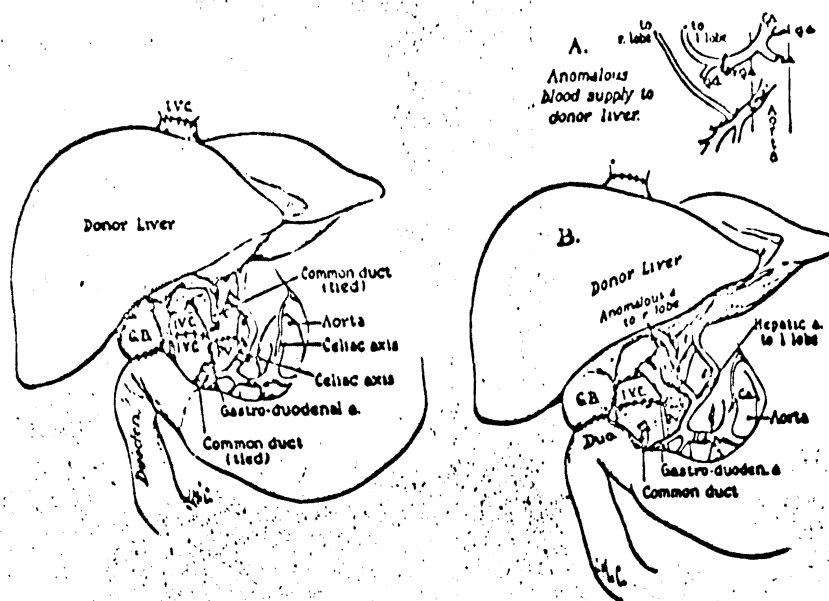


FIG. 2

The figure 2 depicts the operation of orthotopic transplantation and some variations that are necessary; for the surgeon it is worth recognising that there is a high incidence of arterial anomalies, perhaps 20 %, in the general population, so that is one takes 20 % for the donor and 20 % for the recipient, the numbers of anomalies that must be dealt with on one side or the other — that is, either in the homograft or the recipient, add up to about 40 %. The picture on the left shows the usual orthotopic operation, in which it is hoped to do a direct anastomosis of the hepatic arterial supply, the portal venous supply and then connect the vena cava above and below the liver, providing biliary drainage with a colecistoduodenostomy. Shown in A and B are some ways in which the homograft anomalies were reconnected, artery or else leaving these connected to the aorta and the attaching the aorta artery or else leaving these connected to the aorta and then attaching the aorta to the side of the recipient aorta. However, if anomalies are encountered either in the donor or in the recipient, it usually spells a difficulty.

Now, I mentioned earlier that there had been a series of futile attempts of orthotopic transplantation until the summer of 1967, and they were futile in the sense that two of the patients — two of the series of nine — at our place, Boston and in Paris, died as a consequence of the operation; the others all died between six and twenty-three days after operation.

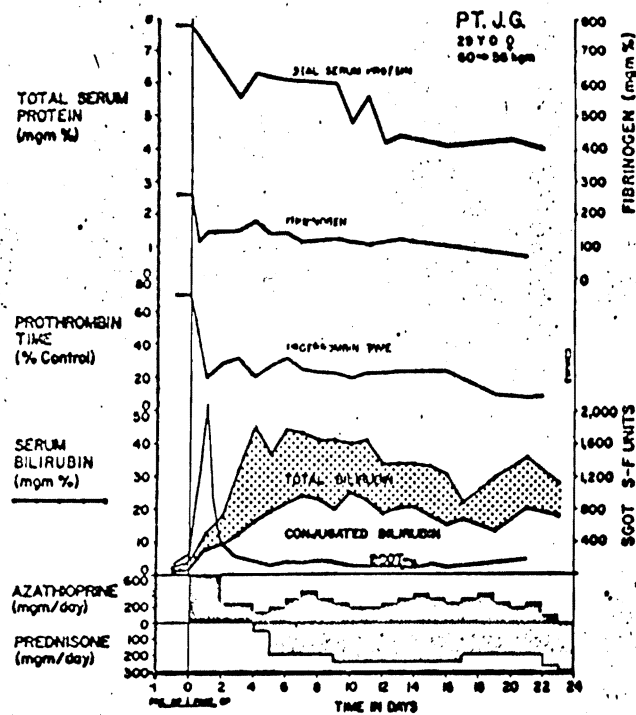


FIG. 3

And this (fig. 3) is a fairly typical picture that is shown here of a very badly damaged liver that was transplanted at the point indicated by the vertical line — very high rises in SGOT and then the development of inexorable jaundice which in this case rose to more than 43 milligrams per cent. The patient then began to recover and ultimately this unfortunate lady died when her common duct anastomosis dehided and she developed biliary peritonitis. She was treated with azathioprine and prednisone.

Now, another thing that was noticed in these early cases in addition to the fact that the badly damaged organs were being used, was that even when acceptable organs were employed, the immuno-suppressive regimen that is shown here, and which has been used with some success with kidney trans-

plantation, was not good enough to maintain permanent good function or chronic function. Moreover, these patients were unable to support standard doses of azathioprine, so that a common terminal complication was the development of leucopenia.

So that the first problem with liver transplantation is the procurement of a very well preserved organ and I think in fact that the needs in liver transplantation are probably greater than those in cardiac transplantation, that is, I think, the tissue is even more sensitive to ischemia.

Tomorrow you will be talking about how death might be defined, and I simply would like to describe a technique that we have used which does not ordinarily require the redefinition of death in terms of irreversible cerebral injury. What is done — and this is not our invariable practice, but what can be done — is to take a patient who has an irreversible cranial cerebral injury to a suitable place, even to the operating room, where the respirator's support is discontinued in exactly the same sense as Pope Pius described in his famous proclamation on this subject: when the heart beat stops, these little cannulae can be inserted into the central abdominal vessels and the patient then placed on a cardio-pulmonary bypass, using a heart-lung machine into which a heat exchanger has been introduced, so that by doing this the brain is dead, the heart has stopped beating. A circulation is restored within a very few moments after death by either criteria, or by both I should say, and the organ is concomitantly cool. It can then be removed at leisure.

The method that I have just described is a very good one as an emergency procedure to protect the organ from deteriorating after death; but what was lacking until fairly recently was the ability to actually preserve the organ for some hours after it had been removed from the body.

This technique was developed by a man working in our laboratory, Dr. Lawrence Brettschneider.

And this (fig. 4) is a schematic drawing showing exactly how the liver is placed within this conservation unit: here is the liver inside the chamber which is cooled to 5° C; the vascular supply in the liver — that is, both the portal vein and hepatic artery are connected to perfusion unit which is primed with diluted blood. The whole unit and specifically the liver are inside a hyperbaric chamber at about 3 atmospheres. With this moderately simple technique, it is possible to preserve the dog liver for 8-24 hours and then have it support life after a transplantation to the recipient.

A method was used in a number of our cases.

Now (fig. 5), this is the course of the first chronic survivor after human liver transplantation. This is the little girl with the hepatoma who received a transplantation at your far left of this critical line. She had a number of post-

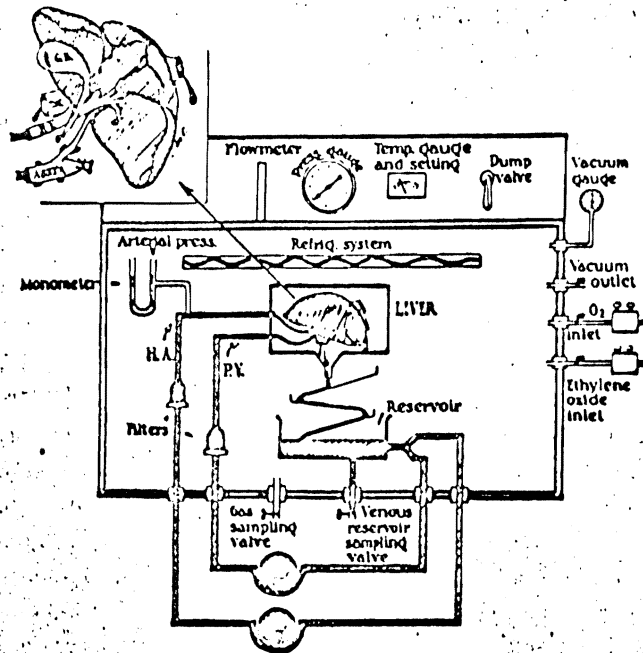


FIG. 4

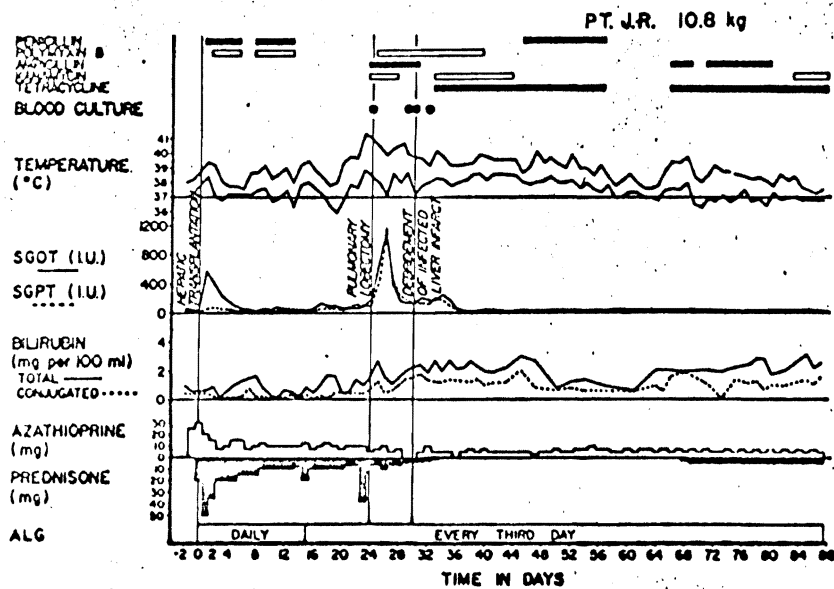


FIG. 5

operative complications that are shown on this slide, but I am afraid the picture contains too much material; but you can get an idea of her situation by glancing across this line which is the bilirubin, and her bilirubins throughout life were in the 0-4 range. Her immuno suppression is shown across the bottom — we won't have time to go into these measures individually, but this is anti-lymphocyte globulin, prednisone and azathioprine. Specifically, I draw your attention to the fact that this little girl and all other livers, in our experience, have received incongruously small doses of azathioprine. Efforts to give them usually more than $\frac{1}{4}$ to $\frac{1}{2}$ milligrams to a kilo — which is a very small dose — have resulted in leucopenia.



FIG. 6

Now, the child — and four other consecutive patients, all pediatric patients, all of them about two years old — developed a specific complication, which I am going to come back to in a moment, or regional infarction or all or part of the right hepatic lobe. When this happened, there were very high increases in SGOT and SGPT. The children developed positive blood cultures, indicated by these vertical crosses, and became extremely febrile.

In the case of this child, she was rescued by De Bredmont of what proved to be necrotic or gangrenous liver tissue; she had problems with sepsis for some months, but eventually lived for about 13 $\frac{1}{2}$ months, finally dying of metastases from the carcinoma for which she was originally treated.

Her chest X-ray after some eight months, showed a tremendous growth of metastatic tumour which invaded the calvarium, the chest and the abdomen. This was her cause of death.

Now, I mentioned earlier that this relatively specific complication of regional hepatic necrosis, which occurred in five straight patients, all children. This could perhaps best be studied by liver scanning. This (fig. 6) shows the

liver scan at 17 days, a PA view and a lateral of this is posterior and anterior: it is completely normal at 17 days, but at 29 days, you see this eroded area on the PA view best seen on a lateral view as large filling defects in the liver. This child had a septicemia at the time and was exceedingly sick.

Here is the picture three days later after these areas were debreeded. At 78 days, you can see that there has been a fairly complete filling in of the defects, both on PA and lateral. This child ultimately regenerated a normal-looking liver.

Now, this complication had never been seen — at least by us — in animals, and we suspected very strongly that the reason was that the hepatic arterial supply was distorted in some way or other, by the fact that the human recipient tries to struggle to its feet, to stand upright, after the operation, whereas the pig and dog, in whom the experimental work was done, has no such tendency. So we did angiography on the next potential donor. That happens to be a five-year-old girl who was killed in an automobile accident. It shows the left hepatic artery, the right hepatic artery — in the supine position. Then we cut the ligaments supporting the liver, a transplantation procedure was simulated. We saw the right hepatic artery appeared to be distorted when the X-ray table is elevated to about a 60° incline. The lobe sways around and down, the artery appears to be kinked. So that, in all subsequent cases, we have very firmly reattached the liver by the suspensory ligaments, the falciform triangular ligaments and so forth, and we have never seen this complication again. It caused the death however, either in a delayed way or ultimately of four of these five patients. The only one who really survived and recovered was the one whose course I have already shown you.

The outcome of this was that, with necrotic liver tissue, the liver was invaded by micro-organism from the intestinal tract and with septicemia.

Now, there has been also moderately high incidence of arterial occlusive accidents in these patients; an angiogram of the child who lived for 13 1/2 months, without hepatic insufficiency, showed the superior mesenteric artery distorted by massive tumor within the abdomen and no direct arterial supply coming from the celiac axis. So this little girl, who clotted off her right hepatic artery initially and presumably at a later time, then clotted her left hepatic artery, was then left only with a portal blood supply, with only a few things coming to the liver from the phrenic artery.

Concerning this matter of vascular thrombosis, there were sixteen recipients of orthotopic transplants that have been treated in Denver prior to two months ago, and of these there were eleven children and five adults. We see that the vascular accidents almost entirely occurred within the pediatric age group — we have not had this kind of access in the adult.

So that, contrary to what has been said, it is our opinion that the adult is the preferred type of recipient for a liver transplantation and not the child.

Another point of considerable importance, we think — at least from a technical point of view — is that there were a disproportionately large number of accidents when a large donor liver was placed in a small recipient; and in this series of some seven there were seven in which the donor weighed from 1 1/2 to 2.3 times as much as recipient. And in this group there were three acute deaths — these deaths all occurred within the first day or two days.

Before I forget to do it, I should say something. It would be worth stopping for just a moment and summarising the results of some of the cases treated in Denver — and I will only report now on those that were operated on at least five months ago, so that there is at least a period of follow-up which has some meaning.

There were 14 patients in all, treated from July 1967 to five months ago, until July 1968. Three of these cases died as the immediate cause of operation, and in all cases there was a vascular accident and the artery clotted or the portal vein clotted. Of the other eleven, there was one who lived for the thirteen plus months and then died of carcinomatosis. There are five more who are living now, after ten and a half, nine and a half, eight, seven and about five months. The other six children — those who died after having survived the operation — died after 35 days, 60 days, 105 days, 134 days and 186 days. Now, four of those five patients died either immediately as a consequence of the right lobe artery thrombosis or as a delayed consequence of that complication, that is, they died because of complex septic problems with big draining sinus tracts in their sides. Those then are the survival statistics.

Now this is a fairly technical course of a patient after liver transplantation: the quality of the liver was satisfactory — it functioned well — several days after operation this patient had a very brisk rejection crisis: the bilirubin rose to about 14 milligrams per cent there were very substantial increases in the alkaline phosphatase and the transaminase; but these proved to be reversible. The patient, a 42-year-old man, whose original disease was a hepatoma was treated about April 1, and has totally normal liver function today. His immuno-suppression was with antilymphocyte globulin, with prednisone, in decreasing doses and with azathioprine; once again remarking about the very small doses which this man received, which were less than 1 milligram per kilo.

Now, I also want to point out another important thing. Antilymphocyte globulin has never been stopped in this patient, a point which we consider of paramount importance, because many of our patients in whom ALG was stopped, have proved to be ALG dependent and then have rejected.

Speaking of some of the findings in rejection, I think you are all aware of the fact that kidneys swell during rejection; perhaps hearts do, but certainly livers do, and it is very easy to detect this with an early post-transplantation scan.

I mentioned earlier a very important point, I think, about cadaveric transplantation of the kidney the liver or the heart, and that is the fact that many such patients — and particularly the liver recipients — have proved to be ALG dependent, so that when ALG was stopped because of severe local reaction, the liver promptly rejected — and many times in fatal way. Once was necessary to remove the first homograft and replace it with a second one; and we think that this is an important case, because it demonstrates that unpaired vital organs: the liver and certainly of course the heart as well, could be replaced on a second occasion if necessary if the first graft rejects. Now, this first procedure was done in May of this year; the second homograft was provided in the middle of July, so that the child is now some five months after receipt of the second organ and a moderately severe rejection can be seen at the beginning of the second homograft, but this has stabilised.